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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/590,026	08/18/2006	Nobuhiro Oikawa	OIKAWA1	5830

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EXAMINER	
RICCI, CRAIG D	

ART UNIT	PAPER NUMBER
1628	

MAIL DATE	DELIVERY MODE
10/14/2009	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/590,026	OIKAWA ET AL.	
	Examiner	Art Unit	
	CRAIG RICCI	1628	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on *09 July 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-3 and 6-11* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) _____ is/are rejected.

7)☒ Claim(s) *1-3, 6-11* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of the Claims

1. The amendments filed 7/09/2009 were entered.

Response to Arguments

2. Applicants' arguments, filed 7/09/2009, have been fully considered. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn. The following rejections and/or objections are either reiterated or newly applied. They constitute the complete set presently being applied to the instant application.

Claim Rejections - 35 USC § 103

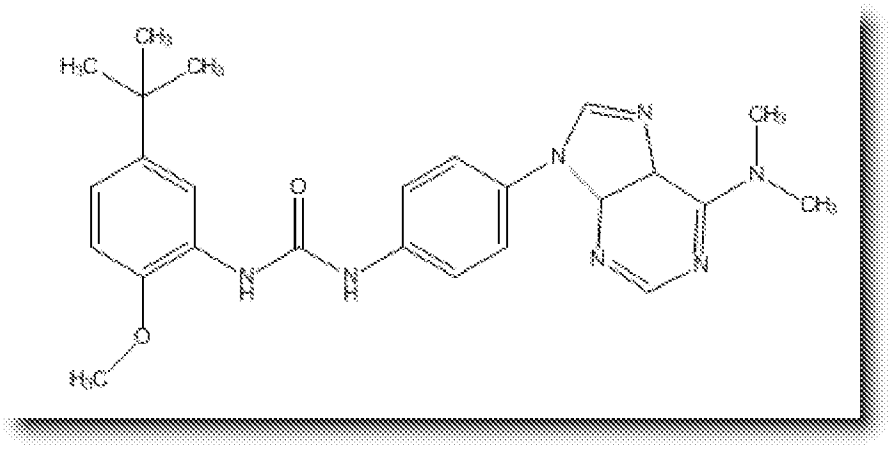
3. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

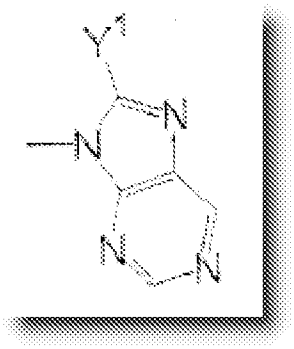
> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

4. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

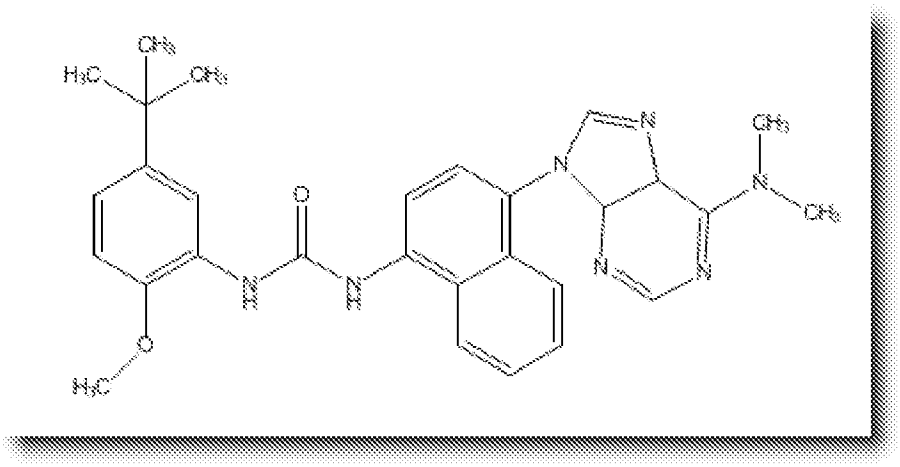
5. **Claims 1 and 7-11 are rejected under 35 U.S.C. 103(a) as being unpatentable over *Cirillo et al* (cited in a previous Action) in view of *Miller et al* (cited in a previous Action).**

6. As discussed in the previous Action, and reiterated herein: instant claim 1 is drawn to compounds of formula (1) which encompass the following compound species:



wherein R^1, R^3 and R^4 are hydrogen; R^2 is a C_1-C_6 alkyl group and R^5 is a C_1-C_6 alkoxy group; Z^1 and Z^2 are hydrogen; R^6 and R^7 are hydrogen; Q is  optionally substituted with W wherein W is –NRaRb (and Ra and Rb are a C_1-C_{10} alkyl) and wherein Y^1 (in Q) is hydrogen, which reads upon claims 1 and 7.

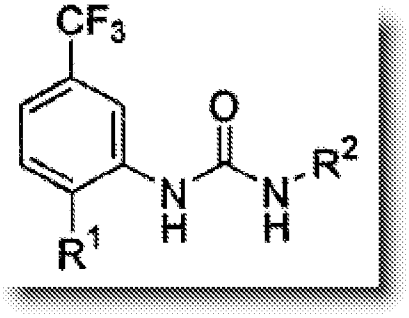
7. *Cirillo et al* teach the following structurally related compound



(The second compound listed on Page 36). Notably, the only difference between the compound taught by *Cirillo et al* and the compound of instant claims 1 and 7 is the substitution of naphthyl (as taught by *Cirillo et al*) for phenyl (as recited by the instant claims). It would have been *prima facie* obvious to a person of ordinary skill in the art at the time the invention was made to substitute naphthyl (as taught by *Cirillo et al*) with phenyl for the following reasons:

8. **FIRST**, it is well known in the art and would have been obvious to a person of ordinary skill in the art at the time the invention was made that phenyl and naphthyl are bioisosteres that can be easily substituted.

9. **SECOND**, *Miller et al* teach structurally related urea compounds



where R^2 can be either phenyl **or** naphthyl (See, for example,

Page 64, Table 2, compare Examples 27 and 28). Accordingly, *Miller et al* teach that structurally related urea compounds having **either naphthyl or phenyl** at the specific point of distinction between *Cirillo et al* and the instant compound species are alternatively usable.

10. As stated by the court in *Aventis Pharma Deutschland GMBH and King Pharmaceuticals, Inc. v Lupin, Ltd.*, No 06-1530 (Fed. Cir. 2007), "[i]n the chemical arts, we have long head that 'structural similarity between claimed and prior art subject matter, proved by combining references or otherwise, where the prior art gives reason or motivation to make the claimed compositions, creates a *prima face* case of obviousness'" citing *Takeda Chem. Indus., Ltd. v. Alphapharm Pty., Ltd.*, No 06-1329 (Fed. Cir. 2007) (quoting *In re Dillon*, 919 F.2d 688, 692 (Fed. Cir. 1990)). And, furthermore, that "[t]he 'reason or motivation' need not be an explicit teaching that the claimed compound will have a particular utility; it is sufficient to show that the claimed and prior art compounds possess a 'sufficiently close relationship… to create an expectation,' in light of the totality of the prior art, that the new compound will have 'similar properties' to the old" citing *Dillon* at 692. "Once such a *prima facie* case is established, it falls to the applicant or patentee to rebut it…" citing *Dillon* at 692. In the instant case, the claimed and prior art compounds are structurally similar, differing in that the compounds taught by the prior art contain a naphthyl group where as the compounds of the instant invention contain a phenyl group. However, a person of ordinary skill in the art at the time the invention was made would have found it obvious to replace naphthyl (in the compounds taught by *Cirillo et al*) with phenyl (as taught by the instant application) in light of the fact that phenyl and naphthyl are well known bioisosteres that can be easily substituted (i.e., phenyl and naphthyl are well known functional equivalents) and further in light of *Miller et al* which specifically teach structurally

related compounds having either naphthyl **or** phenyl are functionally equivalent and are thus either group is alternatively useable, and the skilled artisan would have reasonably expected the new compound to possess similar properties to the old compound.

11. Applicants, however, argue that "the pharmacological effects of the Cirillo compounds are quite different from those of the Miller compounds. Because of these pharmacological differences, there is no reason for one skilled in the art at the priority date to combine Cirillo with Miller… That is, because the Cirillo compounds have such different pharmacological activity from the Miller compounds, one skilled in the art would not expect that substituting the phenyl of Miller for the naphthyl of Cirillo and expect that the compounds would have Raf kinase inhibitory, since the Cirillo compounds are anti-inflammatories" (Applicant Argument, Page 12). **First**, it is noted that the skilled artisan would have been motivated to modify the compound taught by *Cirillo et al* in order to make compounds having similar activity as those taught by *Cirillo et al*. In doing so, the skilled artisan would have found it obvious to substitute naphthyl for phenyl since (A) naphthyl and phenyl are known bioisosteres and (B) *Miller et al* specifically identify napthyl and phenyl as alternatively usable in structurally related compounds. Accordingly, it would have been *prima facie* obvious to modify the compound taught by *Cirillo et al* to arrive at the instantly claimed compound discussed above with the reasonable expectation that such modification would provide a compound having activity similar to the compound disclosed by *Cirillo et al* (i.e., anti-inflammatory activity). Since instant claims 1 and 7 are drawn to compounds, and not methods of using the compounds for inhibition of Raf activity, for example, Applicants' arguments that the skilled artisan would not have expected the compounds to have Raf activity is not considered relevant. **Furthermore**, it is not found persuasive that the

skilled artisan would not have expected the compounds to have Raf activity. Even though it does not appear that *Cirillo et al* necessarily recognized their compounds as Raf kinase inhibitors, the skilled artisan, in view of *Miller et al*, would have predicted such activity. This is because Miller et al teach structurally related compounds which have Raf kinase inhibitory activity. As noted by the court in *Takeda Chemical Industries, LTD. V. Alphapharm PTY., LTD.*, 492 F.3d 1350, citing *In re Deuel*, 51 F.3d 1552 (Fed. Cir. 1995), "close or established '[s]tructural relationships may provide the requisite motivation or suggestion to modify known compounds to obtain new compounds.' A known compound may suggest its homolog, analog, or isomer because such compounds 'often have similar properties and therefor chemists of ordinary skill would ordinarily contemplate making them to try to obtain compounds with improved properties.'" (at page 1356). In other words, compounds which are structurally similar are presumed to possess similar properties. Accordingly, the skilled artisan, noting the structural similarity between the compounds taught by *Cirillo et al* and *Miller et al*, would have reasonably predicted that the compounds taught by *Cirillo et al* would possess Raf kinase inhibitory activity, even though *Cirillo et al* did not disclose such activity.

12. Thus, in view of the foregoing, the rejection of claims 1 and 7 is maintained.

13. Instant claim 9 is drawn to "a pharmaceutical composition comprising a compound… of claim 1 as an active ingredient" (claim 9). *Cirillo et al* specifically teach that "Compounds of the invention may be physically combined with the conventional therapeutics or other adjuvants into a single pharmaceutical composition" (Page 44, Lines 24-26).

14. Instant claims 8 and 10-11 are drawn to the compound of claim 1 which "has Raf inhibiting effect and angiogenesis inhibiting effect and is used for treating… atherosclerosis" etc

(claim 8); is a "raf inhibitor or an angiogenesis inhibitor" (claim 10); and is a "therapeutic agent for a disease selected from… atherosclerosis" etc (claim 11). Applicant is advised that such intended use limitations within product claims do not carry patentable weight. As stated by MPEP 2111.02:

> If the body of a claim fully and intrinsically sets forth all of the limitations of the claimed invention, and the preamble merely states, for example, the purpose or intended use of the invention, rather than any distinct definition of any of the claimed invention's limitations, then the preamble is not considered a limitation and is of no significance to claim construction. *Pitney Bowes, Inc. v. Hewlett-Packard Co.*, 182 F.3d 1298, 1305, 51 USPQ2d 1161, 1165 (Fed. Cir. 1999).

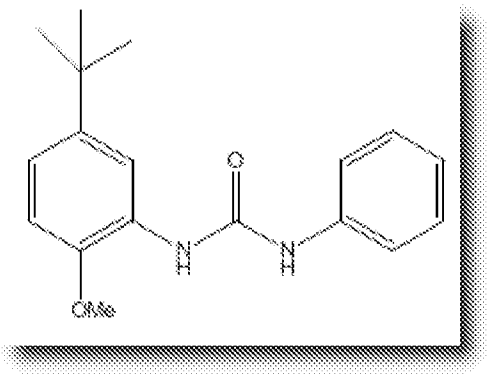
The body of instant claims 8 and 10-11, which are drawn to compositions comprising the compound of instant claim 1 as an active ingredient, clearly set forth all of the limitations of the claimed invention. Accordingly, the purpose and intended uses recited by the claims carry no patentable weight. Claims 8 and 10-11 are thus *prima facie* obvious for the same reasons as applied to instant claim 9 above. Furthermore, *assuming arguendo* that such use limitations did carry patentable weight, absent evidence to the contrary, it is asserted that the *prima facie* obvious compound taught above would necessarily function as a Raf inhibitor and an angiogenesis inhibitor useful for the treatment of atherosclerosis. Indeed, *Cirillo et al* specifically teach that the compounds are useful for the treatment of atherosclerosis (Page 43, Line 9) and the structurally similar compounds taught by *Miller et al* relates to the use of a group of aryl ureas in treating raf mediated diseases and pharmaceutical compositions for use in such therapy" (Page 1, Lines 12-13); more specifically, "compounds which are inhibitors of the enzyme raf kinase" (Page 2,

Lines 6-7). "Where... the claimed and prior art products are identical or substantially identical... the PTO can require an applicant to prove that the prior art products do not necessarily or inherently posses the characteristics of his claimed product. Whether the rejected is based on 'inherency' under 35 USC 102, on '*prima facie* obviousness' under 35 USC 103, jointly or alternatively, the burden of proof is the same, and its fairness is evidenced by the PTO's inability to manufacture products or to obtain and compare prior art products" *In re Best, Boiton, and Shaw* 195 USPQ 430, 433, 562 F2d 1252 (CCPA 1977).

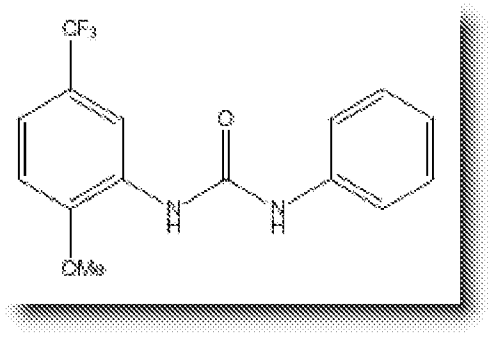
15. Since Applicants do not offer any additional traversals beyond those already discussed above, the rejection of claims 8-11 is also maintained. However, concerning claims 8 and 10, since these claims are drawn to compounds and compositions having the specified activity of inhibiting Raf, evidence of unexpected results may overcome the rejection. For example, evidence that the instant compounds (which one would reasonably predict to inhibit Raf for the reasons discussed above) are unexpectedly superior than what the skilled artisan would have predicted. However, Applicant is reminded that the claims must be commensurate in scope with the unexpected results in order to overcome an obviousness rejection. Currently, the claims are not so limited.

16. **Claims 2-3 and 6 are rejected under 35 U.S.C. 103(a) as being unpatentable over *Cirillo et al* (cited in a previous action) in view of *Miller et al* (cited in a previous action) as applied to claim 1 above, in further view of *Curtin et al* (cited in a previous action).**

17. Instant claims 2-3 and 6 are drawn to the compound of claim 1 wherein R^2 is halogen, a trifluoromethyl group or a triluromethoxy group (claims 2-3) or wherein R^1-R^5 are each independently selected from a hydrogen atom, a chlorine atom, a fluorine atom, a bromine atom

and a trilfluoromethyl group (claim 6). As discussed above, *Cirillo et al* in view of *Miller et al* teach compounds of instant claim 1. Furthermore, *Miller et al* teach compounds having each of the following cores:  (Page 62, Table I)

and

 (Page 64, Table 2).

18. Additionally, *Curtin et al* teach structurally related kinase inhibitors wherein R^1-R^5 on the terminal phenyl are each selected from a hydrogen atom, a chlorine atom, a fluorine atom, a trifluoromethyl group and a C1-C3 alkyl or alkoxy group. As evidenced by *Curtin et al*, trifluoromethyl and hydrogen are significantly more active as kinase inhibitors than alkoxy and hydrogen (Page 4507, Table 2, compare Compound 4e with Compound 4j).

19. Accordingly, one of ordinary skill in the art would have been motivated to substitute the terminal phenyl substituents taught by *Cirillo et al* (which teach compounds having alkoxy and alkyl substituents) with trifluoromethyl in view of *Miller et al* which specifically teach

structurally related compounds having either substitution are functionally equivalent and are thus either group is alternatively useable in phenyl urea compounds. The simple substitution of one known element for another to obtain predictable results is *prima facie* obvious. Furthermore, a person of ordinary skill in the art at the time the invention was made would have been motivated to make compounds encompassed by instant claims 2-3 and 6 as taught by *Curtin et al* (Page 4507, Table 2, Compound 4e and 4o) since the recited substituents provided increased kinase inhibitory activity when compared to compounds containing alkyl or alkoxy substituents. Accordingly, the skilled artisan would have been motivated to make the substitutions encompassed by instant claims 2-3 and 6 in an effort to increase the activity of the compounds and with a reasonable expectation of success.

20. Applicants traverse on the grounds that *Curtin et al* is not available as prior art. Yet, as previously discussed, the earliest effective filing date afforded the instantly claimed invention has been determined to be 02/23/2005 as to claims. While acknowledgment is made of Applicant's claims for foreign priority pursuant to 35 U.S.C. 119(a) and 365(b) based on prior applications filed in Japan on 02/23/2004 and 08/27/2004, the certified copies have **NOT** been received. Accordingly, *Curtin et al* is currently available as prior art.

Conclusion

No new ground(s) of rejection are presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO

MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to CRAIG RICCI whose telephone number is (571) 270-5864. The examiner can normally be reached on Monday through Thursday, and every other Friday, 7:30 am - 5:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Brandon Fetterolf can be reached on (571) 272-2919. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/CRAIG RICCI/
Examiner, Art Unit 1614

/Ardin Marschel/
Supervisory Patent Examiner, Art Unit 1614